Original Article
Clinical Microbiology

Ann Lab Med 2021;41:455-462
https://doi.org/10.3343/alm.2021.41.5.455
ISSN 2234-3806 • eISSN 2234-3814

ANNALS OF LABORATORY MEDICINE

Risk Factors for Extended-Spectrum-β-Lactamase-Producing *Escherichia coli* in Community-Onset Bloodstream Infection: Impact on Long-Term Care Hospitals in Korea

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Background: The prevalence of extended-spectrum β-lactamase-producing *Escherichia coli* (ESBL-EC) in the community has increased worldwide due to multifactorial reasons. ESBL-EC bloodstream infection (BSI) complicates the decision for proper antimicrobial administration. In this multicenter study, we investigated the prevalence, risk factors, and molecular background of community-onset (CO) ESBL-EC BSI.

Methods: We included data for all episodes of ESBL-EC BSI of community origin from May 2016 to April 2017 obtained from the Korean national antimicrobial resistance surveillance system, which comprises six sentinel hospitals. Data, including previous history of admission and use of antimicrobials and medical devices before BSI, were collected, along with microbiological analysis results.

Results: Among 1,189 patients with CO BSI caused by *E. coli*, 316 (27%) were identified as ESBL producers. History of admission, especially to a long-term care hospital (LTCH), and previous use of β-lactams/β-lactamase inhibitors, carbapenem, lincosamide, aminoglycoside, and extended-spectrum cephalosporin were independent risk factors for CO ESBL-EC BSI; admission to an LTCH showed the highest odds ratio (3.8, 95% confidence interval 2.3–6.1). The most common genotype was CTX-M-15 (N=131, 41%), followed by CTX-M-14 (N=86, 27%). ST131 was the most common sequence type among ESBL-EC groups (57%).

Conclusions: In Korea, 27% of CO *E. coli* BSI were caused by ESBL producers. From perspectives of empirical treatment and infection control, history of admission to an LTCH and antimicrobial use should be noted.

Key Words: Community-onset infection, Extended-spectrum β-lactamase-producing *Escherichia coli*, Bloodstream infection, Prevalence, Risk factors, Molecular background

Received: August 10, 2020
Revision received: November 2, 2020
Accepted: March 20, 2021

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INTRODUCTION

Extended-spectrum β-lactamase (ESBL)-producing *Escherichia coli* (ESBL-EC) has emerged as a major antimicrobial-resistant pathogen in the community worldwide [1]. Since ESBLs are typically plasmid-mediated, acquisition of plasmids containing these genes could confer resistance to antimicrobials [2]. SHV and TEM types were the first ESBLs identified in the late 1980s; however, the noble CTX-M type ESBL has dominated since the 1990s [3]. Currently, ESBL-EC spread is mainly caused by the CTX-M-type ESBL-producing sequence type (ST) 131, which could pose a challenge for the management of community-onset (CO) infection [4]. The rapid dissemination of ESBL-EC is likely caused by several factors, such as misuse or overuse of antimicrobials in both humans and animals, international travel, and direct transmission within households and the community [5]. The elucidation of CO BSIs risk factors caused by antimicrobial-resistant bacteria is particularly important and can help develop specific strategies to prevent these infections and the spread of resistant bacteria. From a clinical perspective, this might help identify patients for whom empirical treatment should include coverage against antimicrobial-resistant infection [6]. As the epidemiological characteristics of ESBL-EC can show significant local variations, multicenter studies are important to obtain comprehensive knowledge of risk factors for infections caused by it. However, there are few large-scale studies of CO bloodstream infection (BSI) caused by ESBL-EC in Korea.

The incidence of CO ESBL-EC BSI was estimated to be 7.3% in Spain (2004–2006) [6], 6.9% in South Korea (2006–2009) [7], 6.1% in the United States (2013) [8], and 55.5% in China (2013–2014) [9]. However, the ESBL-EC incidence has increased among community-acquired urinary tract infections [10].

We investigated the prevalence, risk factors, and molecular background of CO ESBL-EC BSI in Korea using data from the Korean antimicrobial surveillance system Kor-GLASS. Kor-GLASS is compatible with the Global Antimicrobial Resistance Surveillance System (GLASS) with respect to the standardization of antimicrobial resistance surveillance, in line with the previous Korean Antimicrobial Resistance Monitoring System [11]. The Kor-GLASS was established in May 2016, and the first 1-year assessment up to April 2017 was published in 2018 [12].

MATERIALS AND METHODS

Study design

Bacterial isolates and clinical data were collected for all episodes of CO ESBL-EC BSI (CO-BSI) from May 2016 to April 2017 in six sentinel hospitals located throughout Korea, with a total of 5,194 beds (715 to 1,050 beds per hospital). During the study period, 1,510 patients were diagnosed as having *E. coli* BSI. Among them, 1,211 patients were identified as having a CO-BSI, which represented 80% of total *E. coli* BSI cases. We excluded 22 patients owing to lack of clinical information, leaving 1,189 patients with CO-BSI for analysis. Data for clinical characteristics, including age, sex, intensive care unit (ICU) admission, underlying illness and its severity (Charlson morbidity index and sequential organ failure assessment [SOFA] score), from the electronic medical records of the sentinel hospitals were investigated [14, 15]. History of admission, antimicrobial use, and use of medical devices before BSI were acquired from the National Health Insurance claims database (HIRA claims data, http://nhiss.nhis.or.kr). Only the first bacterial isolate from each patient was collected for microbiological analysis, and subsequent isolates were excluded. All isolates collected at the sentinel hospitals were transferred to the Research Institute of Bacterial Resistance, Yonsei University College of Medicine, for microbiological assessments.

Phenotypic confirmatory analysis and multilocus sequence typing (MLST) were conducted for each *E. coli* isolate at the analysis center. The study was approved by all local Institutional Review Boards of the six sentinel hospitals included in the study (National Health Insurance Service Ilsan Hospital, Yonsei University College of Medicine, Yonsei University Wonju College of Medicine, Chonnam National University School of Medicine, Inje University College of Medicine, and Chungbuk National University College of Medicine). The requirement for written informed consent was waived.

Definitions

CO-BSI includes healthcare-associated and community-acquired infection but excludes hospital-acquired infection [13]. Cases for which the specimen was taken either from an outpatient or from a patient hospitalized for <two days were included. If a patient was transferred from another hospital, the date of transfer was counted from the admission date at the previous hospital. History of admission was included when a patient was admitted to any hospital, excluding a nursing home, within three months before BSI. History of antimicrobial use was defined as any use of antimicrobials within three months before BSI.

Microbiological analysis

EC identification was performed with matrix-assisted laser de-

https://doi.org/10.3343/alm.2021.41.5.455

sorption/ionization time-of-flight (MALDI-TOF) mass spectrometry (Bruker Biotyper, Bruker Daltonics GmbH, Bremen, Germany) at the analysis center. Susceptibility was analyzed by the disk diffusion method on Mueller-Hinton agar (Difco Laboratories, Detroit, MI, USA), according to the CLSI guidelines [14]. Genes encoding ESBLs (CTX-M-1, CTX-M-9, CTX-M-2, CTX-M25, TEM, and SHV) were analyzed by PCR [15] and sequencing [16]. Briefly, bacterial DNA was extracted by the boiling lysis method, and the PCR was performed under the following amplification conditions: 94°C for 5 minutes, followed by 35 cycles at 94°C for 30 seconds, then 59°C for 30 seconds (bla_{TEM}), 61°C for 30 seconds (bla_{SHV}), or 56°C for 20 seconds (bla_{CTX-M}), and subsequently 72°C for 30 seconds, followed by a final extension at 72°C for 4 minutes using C1000TM Thermal Cycler (Bio-rad, Hercules, USA). PCR amplicons were purified using a QIAquick PCR purification kit (Qiagen, Hilden, Germany) and sequenced using an Applied Biosystems 3730xl DNA analyzer (Applied Biosystems, Foster City, CA) to identify the variant types of each family. MLST was performed on ESBL-EC isolates using seven conserved housekeeping genes (*adk, fumC, gyrB, icd, mdh, purA*, and *recA*) to identify the STs [17], with reference to the EC MLST database (http://mlst.warwick.ac.uk/mlst/dbs/Ecoli).

Statistical analysis

Fisher's exact test was used for univariate comparisons of categorical data. Variables that were not normally distributed, such as age, Charlson comorbidity index, and SOFA score, were analyzed by Mann–Whitney *U* test. Variables with $P<0.05$ from the univariate analysis were included in the multivariate logistic regression model using the Backward Stepwise (Wald) method. We used two multivariate models because of collinearity between variables: history of admission to any hospital and to a long-term care hospital (LTCH). All *P* values were two-tailed and a *P*-value <0.05 was considered to indicate statistical significane. All statistical analyses were performed using IBM SPSS Statistics for Windows software version 23.0 (IBM Corp., Armonk, NY, USA).

RESULTS

The median age of the patients was 75 years [interquartile range (IQR) 63–81 years], and 39% patients (465/1,189) were males. The most prevalent underlying disease was diabetes mellitus (16%, 194/1,189). The median number of antimicrobials used within three months in patients with CO-BSI was 1 (IQR 0–3), and 61% of patients used one or more antimicrobials. The most frequently used antimicrobial was extended-spectrum cephalosporin (29%, 342/1,189), followed by fluoroquinolone (24%) and β-lactams and β-lactamase inhibitors (19%).

Among *E. coli* causing CO-BSI episodes, 316 were identified as ESBL producers, resulting in an ESBL-EC prevalence of 27% (95% confidence interval, [CI] 24–29%). The clinical characteristics of patients with CO-BSI caused by ESBL-EC and non-ESBL-EC isolates are given in Table 1. Of the patients with ESBL-EC, 62% (196/316) had a history of admission to any type of hospital, whereas 40% (346/873) of the non-ESBL-EC patients had a history of hospital admission. Admission to LTCH within three months of BSI was more common in the ESBL-EC group than in the non-ESBL-EC group (13% vs. 4%). There was no statistically significant difference in comorbidities, including diabetes, Charlson comorbidity index, and SOFA score, between the groups.

Univariate logistic regression showed that risk factors of ESBL-EC BSI over those for non-ESBL-EC BSI included a history of ICU admission, history of admission to any hospital and to an LTCH, use of antimicrobials (β-lactams/β-lactamase inhibitors, fluoroquinolone, trimethoprim/sulfamethoxazole, lincosamide, glycopeptide, aminoglycoside, carbapenem, and cephalosporin, regardless of generation), and history of specific intervention (urinary catheterization, nasogastric tubes, and major surgery).

Multivariate analysis of risk factors associated with CO ESBL-EC-BSI is described in Table 2. In the first model, we included a history of admission to any hospital as a variable, whereas the second model included history of admission to an LTCH instead of any hospital, because of recent concerns about antimicrobial resistance in LTCHs in Korea [21]. In the first model, independent risk factors were history of admission to any hospital (odds ratio [OR] 1.6, 95% CI 1.1–2.2) and previous use of carbapenem (OR 2.7, 95% CI 1.7–4.3), lincosamide (OR 2.6, 95% CI 1.3–5.3), aminoglycoside (OR 1.8, 95% CI 1.1–2.7), and extended-spectrum cephalosporin (OR 1.5, 95% CI 1.1–2.2). In addition to these variables, the second model identified the history of admission to an LTCH (OR 3.8, 95% CI 2.3–6.1) and previous use of β-lactams/β-lactamase inhibitors (OR 1.4, 95% CI 1.0–2.0) as significant independent risk factors.

All 316 isolates from patients with confirmed ESBL-EC BSI produced at least one CTX-M enzyme, including 168 (53%) isolates of the CTX-M-1 group and 160 (51%) isolates of the CTX-M-9 group; 12 isolates produced both CTX-M-1 and CTX-M-9 enzymes. The most common genotype was CTX-M-15 (41%, N=131 of ESBL-EC), followed by CTX-M-14 (27%, N=86), CTX-M-27 (N=42), CTX-M-55 (N=28), CTX-M-17 (N=8), and CTX-M-24 (N=6). One isolate produced both CTX-M-15 and

Table 1. Univariate analysis of risk factors associated with community-onset *E. coli* bloodstream infection

Variables	ESBL (N=316)	Non-ESBL (N=873)	OR (95% CI)	*P*
Age (yr), median (IQR)	75 (63–81)	74 (63–81)		0.595
Male	121 (38)	344 (39)	1.0 (0.8–1.2)	0.737
ICU admission	**30 (10)**	**35 (4)**	**2.5 (1.5–4.2)**	**<0.001**
History of hospital admission	**196 (62)**	**346 (40)**	**2.5 (1.9–3.2)**	**<0.001**
History of LTCH admission	**41 (13)**	**37 (4)**	**3.4 (2.1–5.4)**	**<0.001**
Underlying disease				
End-stage renal disease	16 (5)	52 (6)	0.8 (0.5–1.5)	0.672
Cerebrovascular disease	7 (2)	15 (2)	1.3 (0.5–3.2)	0.626
Liver cirrhosis	9 (3)	29 (3)	0.9 (0.4–1.8)	0.852
Chronic pulmonary disease	5 (2)	9 (1)	1.5 (0.5–4.6)	0.542
Diabetes mellitus	62 (20)	132 (15)	1.4 (1.0–1.9)	0.075
Cardiovascular disease	9 (3)	25 (3)	1.0 (0.5–2.2)	1.000
Malignancy	40 (13)	120 (14)	0.9 (0.6–1.3)	0.701
Charlson comorbidity index (median, IQR)	4 (3–5)	4 (3–5)		0.905
SOFA score (median, IQR)	3 (1–5)	3 (1–5)		0.109
Antimicrobial use within previous three months				
Penicillin	19 (6)	50 (6)	1.1 (0.6–1.8)	0.888
β-lactam/β-lactamase inhibitor	**90 (29)**	**135 (16)**	**2.2 (1.6–3.0)**	**<0.001**
Fluoroquinolone	**107 (34)**	**174 (20)**	**2.1 (1.5–2.7)**	**<0.001**
Trimethoprim/sulfamethoxazole	**10 (3)**	**10 (1)**	**2.8 (1.2–6.8)**	**0.022**
Macrolide	22 (7)	39 (5)	1.6 (0.9–2.7)	0.101
Lincosamide	**18 (6)**	**19 (2)**	**2.7 (1.4–5.2)**	**0.004**
Glycopeptide	**16 (5)**	**21 (2)**	**2.2 (1.1–4.2)**	**0.024**
Aminoglycoside	**40 (13)**	**57 (7)**	**2.1 (1.4–3.2)**	**0.001**
Carbapenem	**61 (19)**	**46 (5)**	**4.3 (2.9–6.5)**	**<0.001**
First-generation cephalosporin	**41 (13)**	**62 (7)**	**2.0 (1.3–3.0)**	**0.002**
Second-generation cephalosporin	**70 (22)**	**132 (15)**	**1.6 (1.2–2.2)**	**0.003**
Extended-spectrum cephalosporin	**137 (43)**	**205 (24)**	**2.5 (1.9–3.3)**	**<0.001**
History of intervention within three months				
Urinary catheterization	**58 (18)**	**80 (9)**	**2.2 (1.5–3.2)**	**<0.001**
Center catheter	18 (6)	32 (4)	1.6 (0.9–2.9)	0.140
Intubation/tracheostomy	3 (1)	6 (1)	1.4 (0.3–5.6)	0.707
Nasogastric tube	**20 (6)**	**26 (3)**	**2.2 (1.2–4.0)**	**0.011**
Major surgery	**13 (4)**	**16 (2)**	**2.3 (1.1–4.8)**	**0.032**

Data are summarized as N (%), unless otherwise indicated.
Bold formatting indicates statistical significance.
Abbreviations: CO, community-onset; ESBL, extended-spectrum β-lactamase; EC, *Escherichia coli*; CI, confidence interval; OR, odds ratio, ICU, intensive care unit; IQR, interquartile range; LTCH, long-term care hospital; SOFA, sequential organ failure assessment.

TEM-30. MLST showed that the 316 ESBL-EC isolates belonged to 65 different STs, suggesting substantial genetic diversity among isolates. ST131 was more common in ESBL-EC (57%) than in non-ESBL-EC (8%) isolates (Table 3).

DISCUSSION

Previous studies indicated that risk factors for CO ESBL-EC infections were related to contact with healthcare facilities (such as recent admission to a hospital, residence in an LTCH), recent

https://doi.org/10.3343/alm.2021.41.5.455

Table 2. Multivariate analysis of risk factors associated with community-onset *E. coli* bloodstream infection

Model	OR (95% CI)	*P*
Model with history of admission to any hospital		
History of admission*	**1.6 (1.1–2.2)**	**0.006**
Previous use of antimicrobials		
Carbapenem	**2.7 (1.7–4.3)**	**<0.001**
Lincosamide	**2.6 (1.3–5.3)**	**0.006**
Aminoglycoside	**1.8 (1.1–2.7)**	**0.014**
Extended-spectrum cephalosporin	**1.5 (1.1–2.2)**	**0.031**
Model with history of admission to LTCH		
History of admission to LTCH*	**3.8 (2.3–6.1)**	**<0.001**
Previous use of antimicrobials		
β-lactam/β-lactamase inhibitor	**1.4 (1.0–2.0)**	**0.039**
Carbapenem	**2.9 (1.8–4.5)**	**<0.001**
Lincosamide	**2.6 (1.3–5.1)**	**0.008**
Aminoglycoside	**1.8 (1.1–2.8)**	**0.015**
Extended-spectrum cephalosporin	**1.7 (1.3–2.4)**	**<0.001**
1st generation cephalosporin	1.5 (0.96–2.4)	0.075

Bold formatting indicates statistical significance.
*These two variables were not analyzed simultaneously because of collinearity.
Abbreviations: LTCH, long-term care hospital; OR, odds ratio.

Table 3. Sequence type of community-onset *E. coli* bloodstream infection

STs	ESBL (N=316)	Non-ESBL (N=873)	Total (N=1,189)	*P*
ST131	181 (57)	72 (8)	253 (21)	<0.001
ST95	5 (2)	119 (14)	124 (10)	
ST69	14 (4)	99 (11)	113 (10)	
ST1193	17 (5)	56 (6)	73 (6)	
ST73	0	62 (7)	62 (5)	
ST38	13 (4)	27 (3)	40 (3)	
Others	86 (27)	438 (50)	524 (44)	

Data are summarized as N (%) of patients.
Abbreviations: ST, sequence type; ESBL, extended-spectrum β-lactamase.

use of medical devices (such as a urinary catheter), recent use of antimicrobial agents, and comorbidities [6, 18, 19]. In this study, previous admission to a hospital, especially to an LTCH, and use of carbapenem, lincosamide, aminoglycoside, and extended-spectrum cephalosporin antimicrobials within the previous three months emerged as risk factors for ESBL-EC BSI, whereas medical procedures, such as urinary catheterization and use of nasogastric tubes, did not. Our results will assist in adjusting local recommendations for the appropriate empirical antimicrobial therapy of this unique population, in the sense that patients with these ESBL-EC infection risk factors would be considered for empirical therapy using antimicrobials with activity against ESBL producers.

The burden of infection and antimicrobial resistance in LTCHs is a significant threat to public health [20, 21]. The primary location of antimicrobial resistant bacteria is tertiary-care hospitals, but the frequent referral and transfer between acute-care hospitals and LCTHs in Korea has led to the spread of antimicrobial resistant bacteria to LTCHs [22, 23], which are particularly vulnerable due to lack of effective infection control strategies [24]. In this study, history of LTCH admission was strongly associated with CO ESBL-EC BSI (OR 3.8, 95% CI 2.3–6.1). Because the influx of ESBL-EC from LTCHs can cause outbreaks in acute-care hospitals, appropriate barrier precautions and active surveillance cultures should be employed during patient transfer, according to cost-effectiveness evaluation findings. In addition, further study on the current status of antimicrobial resistance in Korean LTCHs is urgently needed.

This multicenter study of six sentinel hospitals located across Korea showed that an alarmingly high proportion (27%) of CO EC-BSIs are caused by ESBL producers. Korea has experienced a significant increase in the proportion of ESBL producers among CO-BSI causing *E. coli*, with a 4.1% increase in 2002–2005 [25] and 9.5% increase in 2006–2009 [7]. Continuous increase of antimicrobials use would increase the prevalence of resistant isolates; however, this correlation is not always obvious due to the complexity of resistance ecology [26]. Among the antimicrobials, previous use of carbapenem was most significantly associated with CO ESBL-EC BSI in both multivariate models ($P<0.001$). This suggests that increased use of carbapenem would increase ESBL producers. To prevent antimicrobial resistance in the community, it is important to focus on antimicrobial stewardship and, in particular, on the proper use of carbapenem. Reducing the use of other antimicrobials, such as lincosamide, aminoglycoside, and extended-spectrum cephalosporin, will also contribute to preventing the spread of ESBL producers in Korea.

All ESBL-EC isolates had CTX-M-type genotypes, including CTX-M-15 (N=131), CTX-M-14 (N=86), CTX-M-27 (N=42), and CTX-M-55 (N=28). CTX-M-15 was the most common type among ESBL-EC from clinical blood isolates at Korean hospitals [27, 28]. CTX-M-55 can be rapidly disseminated and transmitted in clinical practices in China [29] and is the most frequently detected ESBL-EC type of animal-origin in Korea [30, 31]. This reflects temporal trends in $bla_{\text{CTX-M}}$ epidemiology, showing that

bla$_{CTX-M}$-15 and *bla*$_{CTX-M}$-14 have displaced other genotypes in many parts of the world [32]. One isolate in our study had both CTX-M-15 and TEM-30.

The MLST results showed clonal diversity among EC isolates, but ST131 was the most common ESBL-EC type; hence, ST131 is another risk factor of ESBL-EC. We previously reported that ST131 clones may be associated with the spread of community-associated BSI exhibiting high antimicrobial resistance and highly virulent H30Rx traits [27]. In a multicenter study from Korea, the prevalence of ST131 isolates was 21% (57/268) [33]. ST131 can harbor CTX-M-14 and CTX-M-15 [27, 31] and was associated with hospital settings but now plays a major role in global dissemination as a pandemic clone, causing predominantly CO antimicrobial-resistant infection [34]. The reasons for the successful dissemination and expansion of the ST131 clones remain unclear, but possible contributors include LTCH [35], mismatched antibiotic selection [36], and the expansion of fluoroquinolone resistance-associated subclones [37]. ESBL-EC spread in communities has led to the increased use of carbapenems, which creates selection pressure for carbapenem resistance. In this superbug era, carbapenem-resistant *Enterobacteriaceae* ST131 warrants close attention with respect to its epidemiological success and high prevalence in community settings. Among the 116 carbapenemase-producing strains collected from 16 countries during 2008–2013, 41 (35%) were carbapenemase-producing ST131 *E. coli* isolates [38].

Many of these risk factors have already been identified in studies from other countries. However, similar studies are needed in other regions, because risk factors might show substantial geographic differences across the world, according to antimicrobial-prescribing practices, rates of colonization in the population, and population density. The strength of this study is that we analyzed CO-associated *E. coli* isolated in Kor-GLASS, based on the principles of representativeness, specialization, harmonization, and localization. The clinical isolates and information from six sentinel hospitals represent four of nine provinces and two of seven metropolitan cities in Korea [12]. We also used HIRA claim data, which include almost all antimicrobials and medical procedures under the National Health Insurance, assuring accuracy in data collection. In conclusion, the prevalence of ESBL-EC is increasing in communities, and 27% of CO EC-BSIs are caused by ESBL producers in Korea. Documented risk factors of CO ESBL-EC BSIs should be considered for empirical treatment, infection control measures, and antimicrobial stewardship.

ACKNOWLEDGEMENTS

We thank all Kor-GLASS participants for their contribution to the program; we especially thank Hyukmin Lee, MD, Ph.D. of Yonsei University (Seoul, Korea) for advice regarding the molecular epidemiology of *E. coli*.

AUTHOR CONTRIBUTIONS

Baek YJ and Kim YA analyzed the data and wrote the manuscript. Kim YA, Kim D, Shin JH, Uh Y, Shin KS, Shin JH, and Jeong SH collected isolates and data. Lee GW, Lee EJ, and Kim DS collected data. Kim D and Jeong SH conducted the microbiological analyses. Park YS contributed to the study conception and manuscript revision. All authors have read and approved the final manuscript.

CONFLICTS OF INTEREST

The authors declare no competing interests.

RESEARCH FUNDING

The study was supported by the research programs funded by the Korea Centers for Disease Control & Prevention (2017E280-401#, PI: YSP; 2017E4400100#, PI: SHJ).

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https://doi.org/10.3343/alm.2021.41.5.455